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\*LIMITED TO MATTERS  
AND PROCEEDINGS BEFORE  
FEDERAL COURTS & AGENCIES  
\*\*REGISTERED PATENT AGENT  
\*\*\*SENIOR COUNSEL

November 9, 2001

WRITER'S DIRECT NUMBER:

(202) 789-5511

Commissioner for Patents  
Washington, D.C. 20231

Art Unit 1655

Re: U.S. Utility Patent Application  
Appl. No. 09/925,313; Filed: August 10, 2001  
For: **An Alpha-2-Macroglobulin Diagnostic Test**  
Inventors: TANZI *et al.*  
Our Ref: 0609.4460004/JAG/HLK

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Information Disclosure Statement;
2. Form PTO-1449 (citing 98 documents - 29 pages);
3. One copy of each of the 98 cited documents: AA1, AB1, AC1, AD1, AE1, AF1, AL1, AM1, AN1, AO1, AP1, AR1, AS1, AT1, AR2, AS2, AT2, AR3, AS3, AT3, AR4, AS4, AT4, AR5, AS5, AT5, AR6, AS6, AT6, AR7, AS7, AT7, AR8, AS8, AT8, AR9, AS9, AT9, AR10, AS10, AT10, AR11, AS11, AT11, AR12, AS12, AT12, AR13, AS13, AT13, AR14, AS14, AT14, AR15, AS15, AT15, AR16, AS16, AT16, AR17, AS17, AT17, AR18, AS18, AT18, AR19, AS19, AT19, AR20, AS20, AT20, AR21, AS21, AT21, AR22, AS22, AT22, AR23, AS23, AT23, AR24, AS24, AT24, AR25, AS25, AT25, AR26, AS26, AT26, AR27, AS27, AT27, AR28, AS28, AT28, AR29, AS29, AT29; and
4. Return postcard.

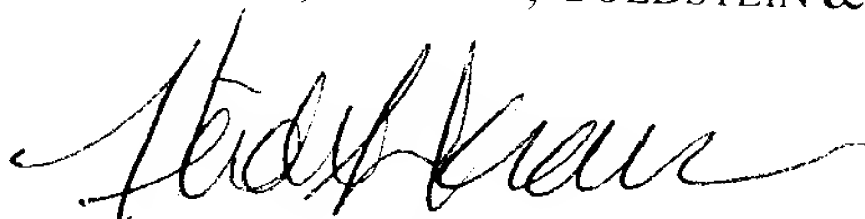
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November 9, 2001  
Page 2

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this letter is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Heidi L. Kraus  
Attorney for Applicants  
Registration No. 43,730

JAG/HLK/rjv  
Enclosures



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Tanzi *et al.*

Appl. No. 09/925,313

Filed: August 10, 2001

For: **An Alpha-2-Macroglobulin  
Diagnostic Test**

Confirmation No.

Art Unit: 1655

Examiner: To be assigned

Atty. Docket: 0609.4460004

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### Information Disclosure Statement

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. A copy of each of these documents is provided.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material

submitted herewith. It is further understood that the Examiner will consider information that had been cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120, 1138 OG 37, 38 (May 19, 1992).

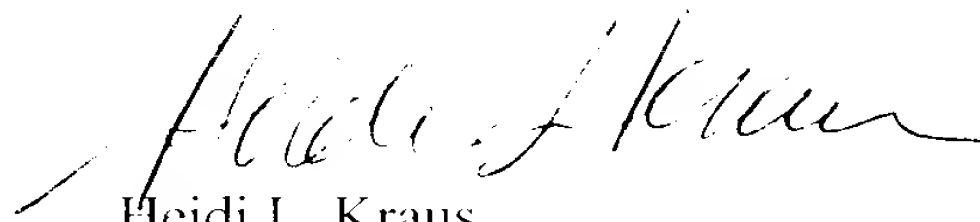
It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449, and to indicate in the official file wrapper of this patent application that the documents have been considered.

This Information Disclosure Statement is being filed within three months of the date of filing of a national application and before the mailing date of a first Office Action on the merits. No statement or fee is required.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Heidi L. Kraus  
Attorney for Applicants  
Registration No. 43,730

Date: November 9, 2001

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FORM PTO-1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0609.4460004	APPLICATION NO. 09/925,313
	APPLICANT Tanzi <i>et al.</i>	
	FILING DATE August 10, 2001	GROUP 1655

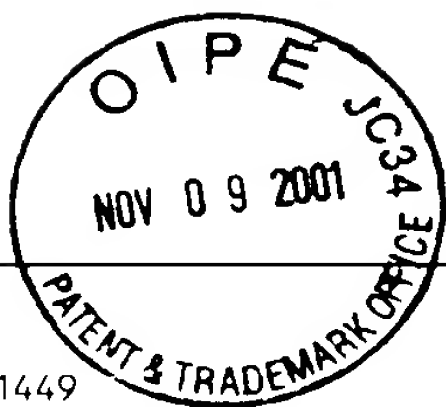
U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA1	4,683,195	07/28/1987	Mullis <i>et al.</i>			
	AB1	5,830,670	11/03/1998	de la Monte <i>et al.</i>			
	AC1	5,948,634	09/07/1999	de la Monte <i>et al.</i>			
	AD1	5,948,888	09/07/1999	de la Monte <i>et al.</i>			
	AE1	6,071,705	06/06/2000	Wands <i>et al.</i>			
	AF1	6,156,311	12/05/2000	Strickland <i>et al.</i>			
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL1	WO 97/04794	02/13/1997	WIPO			Yes No
	AM1	WO 91/03557	03/21/1991	WIPO			Yes No
	AN1	WO 92/03474	03/05/1992	WIPO			Yes No
	AO1	WO 96/39834	12/19/1996	WIPO			Yes No
	AP1	WO 99/11824	03/11/1999	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	1	Alvarez, V., <i>et al.</i> , "Association between an $\gamma$ Macroglobulin DNA Polymorphism and Late-Onset Alzheimer's Disease," <i>Alzheimer's Disease</i> , pp. 48-50, Academic Press, Inc. (October 1999).	
AS	1	Andersen, G.R., <i>et al.</i> , "Low Resolution X-Ray Structure of Human Methylamine-treated $\gamma$ Macroglobulin," <i>J. Biol. Chem.</i> 270:25133-25151, The American Society for Biochemistry and Molecular Biology (1995).	
AT	1	Barrett, A.J., <i>et al.</i> , "The Electrophoretically 'Slow' and 'Fast' Forms of the $\gamma$ Macroglobulin Molecule," <i>Immunology</i> 36:401-418, Portland Press (1979).	

EXAMINER	DATE CONSIDERED
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EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.



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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>2</u>	Bauer, J., et al., "Interleukin-6 and $\alpha$ -2-macroglobulin indicate an acute-phase state in Alzheimer's disease cortices," <i>Alzheimer's Disease</i> 111-114 Elsevier Science B.V. (1991).
	AS	<u>2</u>	Blacker, D., et al., "Alpha-2 macroglobulin is genetically associated with Alzheimer disease," <i>Nature</i> 357-360, Nature Publishing Group (1998).
	AT	<u>2</u>	Blacker, D., et al., "Alpha-2 macroglobulin is genetically associated with Alzheimer disease," <i>Nature</i> 357-360, Nature Publishing Group (May 1999).

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	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>3</u>	Blennow, K., et al., "No association between the $\alpha$ 2-macroglobulin (A2M) deletion and Alzheimer's disease, and no change in A2M mRNA, protein, or protein expression," <i>Journal of Neurology</i> 247:1065-1079, Springer-Verlag (August 2000).
	AS	<u>3</u>	Boado, R.J., "Antisense drug delivery through the blood-brain barrier," <i>Adv. Drug Delivery Rev.</i> 15:73-107, Elsevier Science (1995).
	AT	<u>3</u>	Boado, R.J., et al., "Drug Delivery of Antisense Molecules to the Brain for Treatment of Alzheimer's Disease and Cerebral AIDS," <i>Journal of Pharmaceutical Sciences</i> 87:1308-1315, American Chemical Society and American Pharmaceutical Association (1998)

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	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>4</u>	Borth, W. "α-Macroglobulin a multifunctional binding protein with targeting characteristics," <i>FASEB J.</i> 6:3345-3353, The Federation of American Societies for Experimental Biology (1992).
	AS	<u>4</u>	Bowen, M.E., and Gettins, P.G.W. "Bait Region Involvement in the Dimer-Dimer Interface of Human α-Macroglobulin and in Mediating Gross Conformational Change," <i>J. Biol. Chem.</i> 273:1825-1831 The American Society for Biochemistry and Molecular Biology, Inc. (1998).
	AT	<u>4</u>	Breitaudiere, J.-P., et al. "Structure of native α-macroglobulin and its transformation to the protease bound form," <i>Ann. NY Acad. Sci.</i> 544:1437-1441, The National Academy of Science (1988).

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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>5</u>	Businaro, R., et al., "Synthesis and secretion of $\alpha_2$ -macroglobulin by human glioma established cell lines," <i>Exp. Brain Res.</i> 88:213-218, Springer-Verlag (1992).
	AS	<u>5</u>	Cavus, I., et al., "Inhibition of Long-term Potentiation Development in Rat Hippocampal Slice by $\alpha_2$ -Macroglobulin, an Acute-Phase Protein in the Brain," <i>J. Neurosci. Res.</i> 44:282-288, Society for Neuroscience (1996).
	AT	<u>5</u>	Chen, L., et al., "Apolipoprotein E promoter and $\alpha_2$ -Macroglobulin polymorphisms are not genetically associated with Chinese late onset Alzheimer's disease," <i>Ann. Neurol.</i> 45:173-177, Elsevier Science (July 1999).

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	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>6</u>	Crawford, F., <i>et al.</i> , "The alpha-2 macroglobulin gene is not associated with Alzheimer's disease in a case-control sample," <i>Neurosci. Lett.</i> 270:133-136, Elsevier Science (August 1999).
	AS	<u>6</u>	Dodel, R.C., <i>et al.</i> , "A2 Macroglobulin and the risk of Alzheimer's disease," <i>Neurology</i> 54:438-442, American Academy of Neurology (January 2000).
	AT	<u>6</u>	Dow, D.J., <i>et al.</i> , "A2 macroglobulin polymorphism and Alzheimer disease risk in the UK," <i>Hum. Genet.</i> 103:16-17, Nature Publishing Group (May 1999).

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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>Z</u>	Du, Y., et al., "α-Macroglobulin as a β-Amyloid Peptide-Binding Plasma Protein," <i>J. Neurochem.</i> 61:299-305, Lippincott-Raven Publishing (1997).
	AS	<u>Z</u>	Du, Y., et al., "α-Macroglobulin Attenuates β-Amyloid Peptide 1-40 Fibril Formation and Associated Neurotoxicity of Cultured Fetal Rat Cortical Neurons," <i>J. Neurochem.</i> 67:1182-1188, Lippincott-Raven Publishing (1998).
	AT	<u>Z</u>	Falkner, B., et al., "Short Antisense Oligonucleotide-mediated Inhibition Is Strongly Dependent on Oligo Length and Concentration but Almost Independent of Location of the Target Sequence," <i>J. Neurochem.</i> 62:16187-16194, The American Society for Biochemistry and Molecular Biology (1994).

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	8	"Freely Associating," <i>Nature Genetics</i> 20:1-2, Nature Publishing Group (May 1999).
	AS	8	Feldman, S.R., et al., "Model of $\alpha$ -Macroglobulin structure and function," <i>Proc. Natl. Acad. Sci. USA</i> 82:5700-5704, The National Academy of Science (1985).
	AT	8	Gauderman, W.J., et al., "Family-Based Association Studies," <i>Am. J. Hum. Genet.</i> 65:31-37, Oxford University Press (1999).

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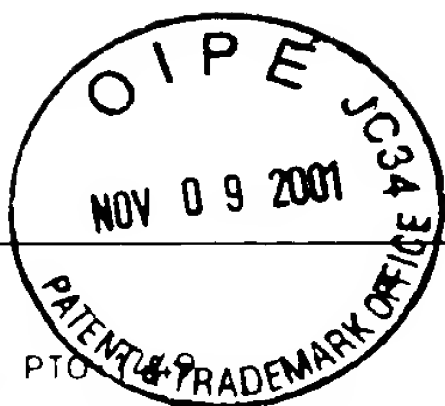
## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	2	Gliemann, J., "Receptors of the Low Density Lipoprotein (LDL) Receptor Family in Man. Multiple Functions of the Large Family Members via Interaction with Complex Ligands," <i>Biol. Chem.</i> 379:951-964, Walter de Gruyter (1998).
	AS	2	Hampe, J., <i>et al.</i> , "Mapping Genes for Polygenic Disorders: Considerations for Study Design in the Complex Trait of Inflammatory Bowel Disease," <i>Hum. Hered.</i> 50:91-101, Karger (March-April 2000).
	AT	2	Hollenbach, E., <i>et al.</i> , "Confirmation of an association between a polymorphism in exon 3 of the low-density lipoprotein receptor-related protein gene and Alzheimer's disease," <i>Neurology</i> 50:1905-1907, Lippincott-Raven Publishers (1998).

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>10</u>	Horvath, S., and Laird, N.M., "A Discordant-Sibship Test for Disequilibrium and Linkage: No Need for Parental Data," <i>Am. J. Hum. Genet.</i> 63:1886-1897, American Society of Human Genetics (1998).
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	AT	<u>10</u>	Jinnah, H.A. and Friedmann, T., "Gene Therapy and the brain," <i>Brain</i> 118:138-148, The British Council (1995).

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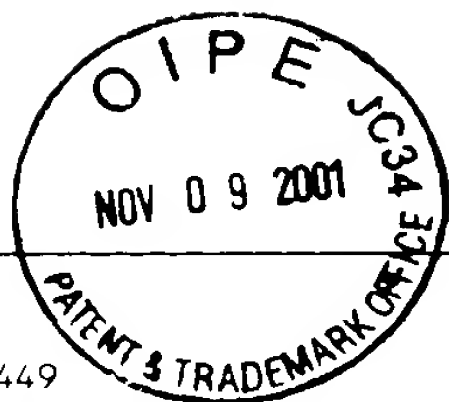
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	AR	<u>11</u>	Justus, C.W.E., et al., "Quantification of free $\alpha$ -macroglobulin and $\alpha$ -macroglobulin-protease complexes by a novel ELISA system based on streptococcal $\alpha$ -macroglobulin receptors," <i>Journal of Immunology</i> 154:103-108, Elsevier Science (1990).
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	AT	<u>11</u>	Kang, D.E., et al., "Genetic association of the low-density lipoprotein receptor-related protein gene (LRP), an apolipoprotein E receptor, with late-onset Alzheimer's disease," <i>Proc. Natl. Acad. Sci. USA</i> 94:56-61, Lippincott-Raven Publishers (1997).

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	AR	<u>12</u>	Kolodziej, S.J., et al., "Three-Dimensional Structure of the Human Plasminogen-Macroglobulin Complex," <i>Biochemistry</i> 37:124-133, Academic Press (1998).
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	AR	<u>13</u>	Kounnas, M.Z., et al., "LDL Receptor-Related Protein, a Multifunctional ApoE Receptor, Binds Secreted $\beta$ -Amyloid Precursor Protein and Mediates Its Degradation," <i>J. Biol. Chem.</i> 270:331-340, Cell Press (1995).
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	AR	<u>14</u>	Kovacs, D.M., et al., "Biological Consequences of the Alpha-2-Macroglobulin-2 Allele Associated with Alzheimer's Disease," A Keystone Symposium on Aging: Genetic and Environmental Influences on Lifes Spans, Tamaron, Colorado (February 1999).
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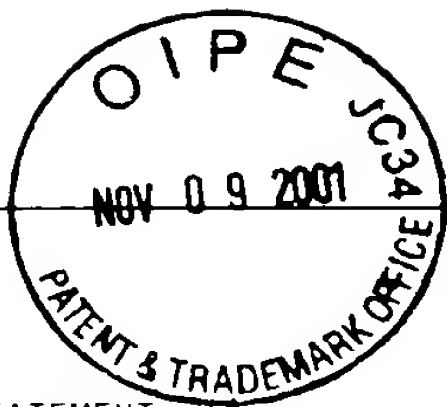
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	AR	<u>15</u>	Kröger, R., et al., "Genetic analysis of the $\alpha$ 2-macroglobulin gene in early- and late-onset Parkinson's disease," <i>Am J Hum Genet</i> 67:2439-2442, Lippincott Williams & Wilkins (August 2000).
	AS	<u>15</u>	Lake, S.L., et al., "Family-Based Tests of Association in the Presence of Linkage," <i>Am J Hum Genet</i> 67:1515-1525, University of Chicago Press (December 2000).
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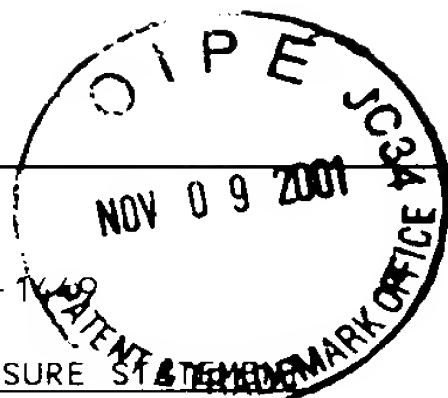
## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>16</u>	Liao, A., et al., "Genetic association of an $\alpha$ 2-macroglobulin (Val1000Ile) polymorphism and Alzheimer's disease," <i>Hum. Mol. Genet.</i> 7:1953-1956, Oxford University Press (1998).
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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>17</u>	Marynen, P., et al., "A Monoclonal Antibody To A Neo-Antigen On $\alpha$ -Macroglobulin Complexes Inhibits Receptor-Mediated Endocytosis," <i>J. Immunol.</i> 136:1782-1786, American Association of Immunologists (1981).
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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	18	Misra, U.K. and Pizzo, S.V., "Binding of Receptor-recognized Forms of $\alpha$ -Macroglobulin to the $\alpha$ -Macroglobulin Signaling Receptor Activates Phosphatidylinositol 3-Kinase," <i>J. Biol. Chem.</i> 273:13399-13402, The American Society for Biochemistry and Molecular Biology (1998).
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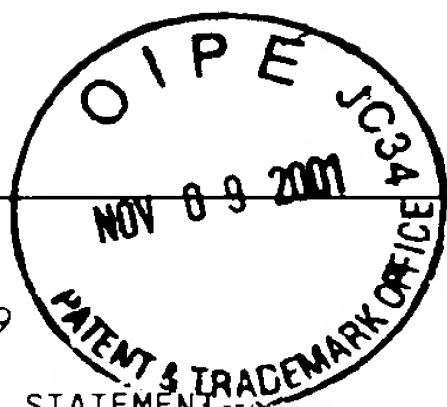
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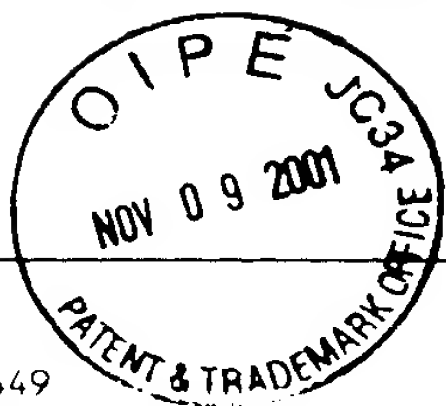
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## U.S. PATENT DOCUMENTS

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>24</u>	Sottrup-Jensen, L., et al., "Primary Structure of Human $\kappa$ -Macroglobulin," <i>Proc. Natl. Acad. Sci. USA</i> 81:8318-8327, The American Society of Biological Chemistry (1984).
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	AT	<u>24</u>	Strauss, S., et al., "Detection of Interleukin-6 and $\kappa$ -Macroglobulin Immunoreactivity in Cortex and Hippocampus of Alzheimer's Disease Patients," <i>Ann. Neurol.</i> 32:223-230 The United States and Canadian Academy of Pathology, Inc. (1992).

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FORM PTO-1449

## INFORMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO.  
0609.4460004APPLICATION NO.  
09/925,313APPLICANT  
Tanzi *et al.*FILING DATE  
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	AR	<u>25</u>	Strickland, D.K., <i>et al.</i> , "Sequence Identity between the $\alpha$ -Macroglobulin Receptor and Low Density Lipoprotein Receptor-related Protein Suggests That This Molecule Is a Multifunctional Receptor," <i>J. Biol. Chem.</i> 265:17401-17404, The American Society for Biochemistry and Molecular Biology (1990).
	AS	<u>25</u>	Strickland, D.K., <i>et al.</i> , "Primary Structure of $\alpha$ -Macroglobulin Receptor-associated Protein," <i>J. Biol. Chem.</i> 266:13364-13369, The American Society for Biochemistry and Molecular Biology (1991).
	AT	<u>25</u>	Tanzi, R., <i>et al.</i> , "Amyloid $\beta$ Protein Gene: cDNA, mRNA Distribution, and Genetic Linkage Near the Alzheimer Locus," <i>Science</i> 238:880-884, American Association for the Advancement of Science (1987).

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FORM PTO-1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0609.4460004	APPLICATION NO. 09/925,313
	APPLICANT Tanzi et al.	
	FILING DATE August 10, 2001	GROUP 1655

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	AR	<u>26</u>	Tanzi, R.E., "A genetic dichotomy model for the inheritance of Alzheimer's disease and common age-related disorders," <i>Ann. N.Y. Acad. Sci.</i> 746:1175-1179, American Society for Clinical Investigation (November 1999).
	AS	<u>26</u>	Tinode, F., et al., "A Conditionally Expressed Third Partner Stabilizes or Prevents the Formation of a Transcriptional Activator in a Three-hybrid System," <i>Proc. Natl. Acad. Sci. USA</i> 94:22995-22999 The American Society for Biochemistry and Molecular Biology (1997).
	AT	<u>26</u>	Tooyama, I., et al., "Immunohistochemical Study of a Macroglobulin Receptor in Alzheimer and Control Postmortem Human Brain," <i>Mol. Brain Res.</i> 18:153-160 Humana Press, Inc. (1993).

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	AR	<u>28</u>	Wavrant-DeVrieze, F., et al., "Association between the low density lipoprotein receptor-related protein (LRP) and Alzheimer's disease," <i>Neuron</i> , 1997, 19:68-70, Elsevier Science Ireland Ltd. (1997).
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	AT	<u>28</u>	Zhang, Z., et al., "Inhibition of alpha-2-macroglobulin/proteinase-mediated degradation of amyloid peptide by apolipoprotein E and alpha-antichymotrypsin," <i>Neuron</i> , 1996, 16:156-161, Parthenon Publishing Group (1996).

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	AR	<u>29</u>	Zill, P., et al., "Polymorphisms in the $\alpha$ -2 macroglobulin gene in psychogeriatric patients," <i>Neurosci Lett</i> , 41:69-72, Elsevier Science Ireland Ltd. (November 2000).
	AS	<u>29</u>	International Search Report for International Application No. PCT/US00/02412, mailed July 6, 2000.
	AT	<u>29</u>	

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